HHS Public Access

Author manuscript

Vaccine. Author manuscript; available in PMC 2019 June 30.

Published in final edited form as:

Vaccine. 2019 May 31; 37(25): 3296–3302. doi:10.1016/j.vaccine.2019.04.080.

Vaccine safety in HIV-infected adults within the Vaccine Safety Datalink Project

Rulin C. Hechter[a,*], **Lei Qian**[a], **Sara Y. Tartof**[a], **Lina S. Sy**[a], **Nicola P. Klein**[b], **Eric Weintraub**[c], **Cheryl Mercado**[a], **Allison Naleway**[d], **Huong Q. McLean**[e], and **Steven J. Jacobsen**[a]

[a]Kaiser Permanente Southern California, USA

[b]Kaiser Permanente Northern California, USA

[c]Immunization Safety Office, Centers for Disease Control and Prevention, USA

[d]Kaiser Permanente Northwest, USA

[e]Marshfield Clinic Research Institute, USA

Abstract

Objectives: We evaluate safety of routine vaccination among adults infected with human immunodeficiency virus (HIV) in five healthcare organizations in the United States.

Methods: We conducted a retrospective cohort study of HIV-infected adults who received inactivated influenza vaccines, hepatitis B vaccines, pneumococcal vaccines, or tetanus, diphtheria, and acellular pertussis vaccines between 2002 and 2013. We conducted self-controlled case series analysis to estimate the relative risk (RR) for 11 pre-specified adverse events (AEs) requiring medical attention.

Results: Among 20,417 HIV-infected adults (90.2% male), a total of 137,674 vaccine doses were administered. Based on ICD-9 codes, we detected an increased risk of cellulitis and infection (RR:

[*]Corresponding author at: Department of Research & Evaluation, Kaiser Permanente Southern California, 100 S. Los Robles, 2nd Floor, Pasadena, CA 91101, USA. Rulin.C.Hechter@kp.org.

Author contributions

Hechter and Qian take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Hechter, Qian, Tartof, Sy, Jacobsen. Acquisition of data: Qian, Sy, Mercado.

Analysis and interpretation of data: Hechter, Qian, Jacobsen, Sy, Tartof, Klein, Weintraub, Naleway, McLean.

Drafting of the manuscript: Hechter.

Critical revision of the manuscript for important intellectual content: all co-authors provided critical review and feedback on the manuscript.

Statistical analysis: Qian.

Administrative, technical, and material support: Sy, Mercado.

Conflicts of interest disclosures

Hechter has received research support from Novartis and GSK for unrelated studies. Tartof has received research support from GSK and Merck for unrelated studies. Sy has received research support from Novartis, GlaxoSmithKline, Novavax, and Dynavax. Klein has received research support from Merck, Pfizer, Sanofi Pasteur, Protein Science (now Sanofi Pasteur), GSK, MedImmune, and Dynavax. Mercado and Jacobsen have received research support from Dynavax. Naleway has received research support from Pfizer and Merck for unrelated studies. Qian, McLean, and Weintraub report no conflict of interest.

Publisher's Disclaimer: CDC disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.04.080.

1.18, 95% CI:1.03–1.35) among all patients, and an increased risk of stroke/cerebrovascular diseases among patients with an HIV viral load >10,000 copies/ml (adjusted RR: 3.94, 95% CI: 1.32–11.72). Further analyses on chart confirmed cases of stroke/cerebrovascular diseases indicated no statistically significant increased risk (adjusted RR: 1.72, 95% CI: 0.41–7.24). There was no evidence of increased risk for other AEs following routine vaccination in HIV-infected adults.

Conclusions: Routinely administered vaccines are generally safe for HIV-infected adults.

Keywords

Vaccine safety; HIV; Vaccine Safety Datalink

1. Introduction

Due to impaired host immune defenses, persons infected with human immunodeficiency virus (HIV) have an increased risk and greater severity of vaccine-preventable infections, resulting in high morbidity and mortality. HIV-infected persons are more susceptible to influenza and experience prolonged duration and increased severity of illness and have higher rates of hospitalization [1–4]. They also have a markedly higher risk of invasive pneumococcal disease despite immune reconstitution and suppression of HIV replication with combination antiretroviral therapy (cART) [5–7]. Individuals with co-infection of HIV and hepatitis B virus (HBV) have increased rates of HBV replication and accelerated disease progression, with increased incidence of liver fibrosis, cirrhosis, end-stage liver disease, hepatocellular carcinoma, and liver-related deaths compared with hepatitis B mono-infected patients [8]. A recent study reported an annual incidence of pertussis among unvaccinated HIV-infected adults of 10.5–17.5% [9]. As CD4+ T helper cells are critical for the clearance of pertussis [10], HIV-infected individuals could have more severe or prolonged pertussis infections than the general population [11–13]. The Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) recommends all HIV-infected adults receive inactivated vaccines against influenza, pneumonia, hepatitis B, and tetanus, diphtheria, and acellular pertussis, regardless of CD4+ T-cell count and age [14–16].

Despite the increased risk for infections and the widespread availability of vaccines, reported vaccine coverage rates among HIV-infected adult patients are low [17–21]. Data from two studies in the United States suggested that influenza vaccination coverage among HIV-infected patients ranged between 25% and 43%, and that patients with a lower CD4+ T-cell count and higher HIV RNA viral load were less likely to have received influenza vaccine [19,20].

Reasons for the low vaccine coverage rates among HIV-infected patients are likely multifactorial [22], including fear of side effects and adverse impact on HIV disease [23]. However, there are no substantive data to support the notion that influenza, pneumococcal, and hepatitis B vaccines adversely affect the overall health of HIV patients or accelerate disease progression [24–30]. Currently, safety data for tetanus-diphtheria and tetanus-diphtheria-acellular pertussis vaccines (Td/Tdap) are not available among HIV-infected

adults. Furthermore, most of the previous vaccine safety studies among HIV-infected patients had small sample sizes and were not powered to detect rare adverse events (AEs). Those previous studies used HIV-uninfected populations as a comparison group, thus estimated risk ratio of vaccine induced AEs is subject to confounding by the effect of impaired immune response in HIV-infected patients because the underlying risks in HIV-infected individuals are expected to be different from that in HIV-uninfected patients.

Within a large, community-based, diverse cohort of HIV-infected adults receiving care from 2002 to 2013, we sought to use an self-controlled study design to examine whether there was an increased risk of pre-specified AEs following receipt of recommended inactivated vaccines for HIV-infected adults, including inactivated influenza vaccine (including monovalent H1N1pdm09 vaccine), 23-valent pneumococcal polysaccharide vaccine (PPSV23) and 13-valent pneumococcal conjugate vaccine (PCV13), HBV vaccine, Td, and Tdap, and to assess whether the risk differed by level of CD4+ T-cell count or HIV RNA viral load at vaccination.

2. Methods

2.1. Study setting

This study was conducted in the population of a multi-site vaccine safety project, Vaccine Safety Datalink (VSD). We have used the large administrative data and electronic health records (EHR) of the VSD to study immunization safety in the United States, which captures comprehensive medical and immunization histories for more than 10.7 million people annually, representing roughly 3% of the population in the United States. Results from this project have been used to inform policymakers and healthcare practitioners about a variety of vaccine safety-related topics. The protocol for this study was reviewed and approved by the Institutional Review Board at each participating site.

2.2. Study design and study population

We included all adults (>18 years) infected with HIV who received at least one of the vaccines of interest (inactivated influenza vaccine, PPSV23, PCV13, HBV vaccine, Td, and Tdap) during January 2002 through December 2013 at five integrated health care organizations of VSD. We identified HIV-infected patients through centralized HIV patient registries in EHR at three participating sites and by positive Western Blot test results at the other two sites. Vaccination information was ascertained through the vaccine file. Continuous membership at the health systems (allowing a 31-day gap for administrative delays) in the one year prior to vaccination was required to allow ascertainment of incident status of AEs. All vaccines administered in the participating sites were recorded in the EHR routinely. Information on vaccines received outside of the healthcare systems were captured through claims data, and as a standard practice, providers routinely collect the information on vaccines received out of the healthcare systems and back enter the information in the EHR. The membership requirement also allowed assessment of the baseline CD4+ T-cell count and HIV RNA viral load measured in the six months prior to and including the date of the vaccination. All information was linked through the patient unique ID.

We used the self-controlled case series (SCCS) design to evaluate the association between vaccination and risk of pre-specified incident acute AEs among eligible HIV-infected patients. An incident AE was defined as a new diagnosis following vaccination, i.e. no history of the same diagnosis in previous 30 days for local allergic reactions and anaphylaxis and in the last 12 months for other severe acute events. In SCCS analyses, each person serves as his/her own comparison: for each AE, a pre-specified risk window was defined following the date of the index vaccination (day 0), and a comparison window was defined as a time period immediately following the risk window. The observational period for each vaccination encounter was censored at membership disenrollment or upon receipt of another vaccine of interest. The SCCS design adjusts for non-time varying confounders, such as sex and race/ethnicity. Given the short follow-up period and the acute nature of the AEs of interest in this study, we can also assume that each individual's age, socioeconomic status (education, income), HIV disease severity level (e.g. CD4+ T-cell count, HIV RNA viral load), status of comorbidities, and cART use did not vary substantially across the risk and control windows.

2.3. Outcomes

The primary outcomes for this study included 11 pre-specified acute AEs after vaccination that were categorized into 5 groups: (1) systemic reactions (anaphylaxis); (2) local reactions (cellulitis and infection, allergic reaction); (3) cardiovascular events (acute and subacute myocardial infarction, acute pericarditis, acute myocarditis, cardiomyopathy, and heart failure); (4) stroke and cerebrovascular diseases, venous thromboembolism (VTE); and (5) meningitis, encephalitis, and encephalopathy. We selected these AEs based on previous vaccine safety studies conducted among general populations. We also included acute cardiovascular events, stroke, cerebrovascular diseases, and VTE to explore whether there is an elevated risk following vaccinations, as people living with HIV may experience an increased risk of vascular disease. The risk window was determined based the estimate of a plausible incubation period between vaccination and the onset of each AE, a method generally used in vaccine safety studies. To be consistent with the previous vaccine safety studies, we defined the risk window for anaphylaxis as 0–6 days. We defined the risk window for local reactions as 1–7 days, and 1–42 days for all other AEs of interest. We excluded diagnosis codes assigned on the day of vaccination (Day 0) from analysis of safety signals for local reactions and other AEs except for anaphylaxis, because diagnosis codes assigned on day 0 usually represent pre-existing conditions based on our experiences in previous VSD studies. For each AE in this study, we defined the comparison window as two times the length of the corresponding risk window immediately following the risk window. The specific AEs, risk windows, International Classification of Diseases, 9th revision (ICD-9) codes, and care settings (inpatient, emergency department [ED], outpatient) used to identify these events are provided in Appendix Table 1.

2.4. Analysis

We calculated the total number and the average number of vaccine doses received per person by vaccine type. We reported the number of incident AEs identified by ICD-9 codes during pre-specified risk and comparison windows. Because each HIV-infected patient served as their own control in the SCCS analysis, we used conditional Poisson regression models to

estimate relative risk (RR) for each AE by comparing the incidence in the risk window vs. the incidence in the comparison window. Multiple doses administered on different dates were treated as repeat exposures with assumption of same risk for each exposure in the analyses [31]. Multiple vaccines administered concomitantly on the same day were treated as one exposure in the main analysis of AE following any vaccination. Concomitant vaccines were accounted for in the subgroup analyses by vaccine type. To account for potential confounding by clustering of seasonal vaccination (e.g., influenza vaccines given during winter months), analyses were adjusted for seasonality for AEs with a risk window ≥ 14 days. Analyses were further stratified by vaccine type, receipt of concomitant vaccines, baseline CD4+ T-cell count (<200, 200–499, ≥500 cells/mm^3), and HIV RNA viral load (undetected or ≤200, 201–10,000, >10,000 copies/ml). The cut-off values of the categorical stratification were determined by the widely used standard ranges for determining the levels of immune function and control of HIV disease (the lower the CD4+ T-cell count, the more severely impaired immune function; the higher the HIV RNA viral load, the worse viral suppression). The 95% confidence intervals (CI) of RRs that did not overlap with 1 were considered statistically significant. Serious outcomes with a statistically significant increased risk were chart reviewed to confirm the diagnosis and symptom onset date. Additional SCCS analyses were conducted based on chart-confirmed AE cases and symptom onset date. We performed statistical analyses using SAS, version 9.3 (SAS Institute, Cary, NC).

3. Results

We identified 20,417 eligible HIV-infected adult vaccinees who received a total of 137,674 vaccine doses on 124,645 unique dates (a person could receive more than one vaccine on one day) during 2002–2013. Most of the HIV-infected patients in this study were males (~90%). The age of HIV-infected patients in this study ranged between 18 and 96 years, with a mean age of 51 years (standard deviation = 11.5). During the study period, the study population received 88,575 doses of influenza vaccine, 12,693 doses of HBV vaccine, 23,092 doses of PPSV23 or PCV13, and 13,314 doses of Td or Tdap. On average, each patient received approximately 7 doses of various vaccines during the study period, with an average of 4.8 doses of influenza vaccine, 2.6 doses of HBV vaccine, 1.5 doses of PPSV23/PCV13, and 1.1 doses of Td/Tdap among those who received any of those vaccines. A CD4+ T-cell count measurement within 6 months prior to vaccination was available for 93.8% of the vaccination dates, and 93.5% had a HIV RNA viral load measurement.

Among all patients receiving any type of vaccine of interest, a small elevated risk for cellulitis and infection in the 1–7 days following vaccination was detected (RR: 1.18, 95% CI: 1.03–1.35) (Table 1). There was no significant increased risk for other AEs following vaccination. In analyses stratified by whether patients received more than one type of vaccine on the same day (i.e., concomitant vaccination, n = 11156, 9% of the total sample), a slightly elevated risk for cellulitis and infection was also observed among patients who did not receive concomitant vaccine (RR: 1.17, 95% CI: 1.02–1.34); while the point estimate of the relative risk among those who received concomitant vaccination was slightly higher, but it was not statistically significant (RR: 1.35, 95% CI: 0.86, 2.11). In stratified analyses by vaccine type (influenza, HBV, or bacterial vaccines including PPSV23/PCV13 and Td/Tdap), an elevated risk for cellulitis and infection was only observed among patients who

received bacterial vaccines (RR: 1.88, 95% CI: 1.48–2.40), while there was no significant risk detected after either influenza vaccination or HBV vaccination. We did not observe an elevated risk of any other AE regardless of concomitant vaccination or the type of vaccine.

Baseline CD4+ T-cell count was < 200 cells/mm^3 in 8% of patients and ≥ 500 cells/mm^3 in 53% of patients. In analyses stratified by baseline CD4+ T-cell count, a small but statistically significant risk for cellulitis was observed among patients with baseline CD4+ T-cell count ≥ 500 cells/mm^3 (RR: 1.25, 95% CI: 1.03–1.52). We also observed a small risk of cellulitis among patients with baseline CD4+ T-cell count < 200 cells/mm^3 (RR: 1.11, 95% CI:0.75–1.65), but the association did not reach statistical significance, potentially due to the small sample size of this subgroup (n = 9,216). No significant elevated risk was identified for other AEs in analyses stratified by baseline CD4+ T-cell count; however, we observed a non-statistically significant elevated risk for stroke and cerebrovascular diseases (adjusted RR: 1.79, 95% CI: 0.65–4.91) among patients with a baseline CD4+ T-cell count < 200 cells/mm^3. In stratified analyses by HIV RNA viral load, we detected a significantly elevated risk for stroke and cerebrovascular diseases (RR: 3.94, 95% CI: 1.32–11.72) among patients with a baseline viral load greater than 10,000 copies/ml, based on data from 11,339 unique vaccination dates (Table 2). There was no elevated risk among those with a baseline viral load < 10,000 copies/ml. When we further stratified the analysis by vaccine type among those who had a baseline HIV RNA viral load greater than 10,000 copies/ml, we observed elevated risks for stroke and cerebrovascular diseases following influenza vaccine, HBV vaccine, and PPSV23/PCV13, but the estimates for adjusted RRs were not statistically significant and the confidence intervals were wide (Table 3). The adjusted RR for stroke and cerebrovascular diseases following Td/Tdap vaccine among those with viral load greater than 10,000 copies/ml was not estimated, as there were no cases identified during the comparison window.

We performed a series of analyses to explore the elevated risk for stroke and cerebrovascular diseases. First, since higher HIV RNA viral load is an indicator for uncontrolled HIV disease and may be associated with other underlying risk factors for stroke, we checked the stability of viral load during time periods across pre-vaccination and post-vaccination periods (including risk and comparison windows, when available). About 90% of the patients had stable viral load values during the one year prior to vaccination and the viral load values were similar in the risk and comparison windows as compared to that prior to vaccination. SCCS analyses stratified by whether patient's viral load remained stable did not alter the results among those with a baseline viral load greater than 10,000 copies/ml (data not shown), and the estimated RRs remained elevated but not statistically significant. Second, we performed separate analyses only on stroke cases based on ICD-9 codes, and still observed an elevated RR in patients with a baseline viral load greater than 10,000 copies/ml (not statistically significant).

Since stroke and cerebrovascular diseases were considered serious AEs following vaccination, we performed manual chart review to confirm the diagnosis and symptom onset date for all stroke and cerebrovascular disease cases identified by ICD-9 codes. Chart review of 131 presumptive cases confirmed 82 as definite cases (62.6%) and 17 (13.0%) as possible cases. Among the 82 confirmed cases, 57 were new-onset cases and 10 were recurrent cases.

Another 15 cases either were coded for a historical diagnosis or lacked information on symptom onset were excluded. Among the confirmed new-onset and recurrent cases (n = 67), 20 cases had a symptom onset date within the risk window, 46 cases had a symptom onset date within the comparison window, and one case was excluded as the symptom onset date was prior to the risk window. None of the confirmed cases had documented HIV treatment regimen change around the time of vaccination or the diagnosis. We then conducted SCCS analyses on the 66 new-onset and recurrent cases confirmed by chart review. The results showed no elevated risk for stroke and cerebrovascular disease following vaccination in the overall cohort (RR: 0.76, 95% CI: 0.51, 1.12) and a RR of 0.53 (95% CI: 0.31–0.90) among patients with achieved viral suppression (viral load ≤ 200 copies/ml), and we observed a RR of 1.72 (95% CI: 0.41–7.24, not statistically significant) for stroke and cerebrovascular disease among patients with the baseline HIV RNA viral load greater than 10,000 copies/ml (Table 4).

We further examined the characteristics of the eight chart-confirmed cases (4 in the risk window on day 0, 12, 36, 39, and 4 in the comparison window on day 70, 74, 95, 105) among patients with baseline viral load greater than 10,000 copies/ml (Appendix Table 2). Among the four cases that occurred in the risk window (two new- onset and two recurrent cases), two of them were stroke cases and two were transient ischemic attack (TIA) cases; while among the four cases in the comparison window (all were new-onset cases), three were stroke cases and one was a TIA case. There was no clustering of timing of onset within the risk and comparison windows by graphically investigating the timing of the events relative to vaccination. All eight cases received either influenza (two cases in the risk window and three cases in the comparison window) or hepatitis B vaccine (two cases in the risk window and one case in the comparison window). Two cases in the risk window and one case in the comparison window had documented evidence of potential risk factors for stroke/cerebrovascular diseases.

4. Discussion

In a large cohort of HIV-infected adults, we found that routinely administered vaccines recommended for HIV-infected adults are generally safe. There was a mild increased risk for cellulitis and infection in the 1–7 days following vaccination, particularly among patients with a baseline CD4+ T-cell count greater than 500 cells/mm^3, and among those who received bacterial vaccines including PPSV23, PCV13, Td and Tdap. A previous VSD study reported an increased risk of inflammatory AEs at the injection site following Tdap vaccination among the general elderly population [32]. A case report described cellulitis-like reaction following PPSV23 vaccination among five adults [33]. In addition, injection site reactions and cellulitis are also listed in the vaccine package insert of some Td, Tdap and pneumococcal vaccines as reported adverse events following vaccination [34]. Our findings of the elevated risk of cellulitis and infection following these vaccines were consistent with those previous reports. We did not find an elevated risk for the other AEs of interest following vaccination in the complete study sample. The findings in this study provided reassurance that those vaccines currently recommended for HIV-infected patients are generally safe.

We did not observe an increased risk of stroke and cerebrovascular diseases among the overall study population. However, a significant elevated risk was detected in analyses based on ICD-9 codes for stroke and cerebrovascular diseases among patients with baseline HIV RNA viral load greater than 10,000 copies/ml. The occurrence of the occurrence of incident stroke and cerebrovascular diseases following vaccination was rare, and we did not observe statistically significant findings in stratified analysis by vaccine type or after we limited the analysis to chart-confirmed new-onset and recurrent cases. The RR point estimate remained greater than 1 (RR = 1.72) with a wide confidence interval in the analysis using chart-confirmed cases, the small sample size may have limited the statistical power to detect a small to moderate risk, thus the wide confidence interval. The risk estimate translated to an absolute risk difference of 4 cases (95% CI: 14–21 cases) per 1,000,000 person-days of follow-up among patients with baseline HIV RNA viral load greater than 10,000 copies/ml. Although the absolute disease burden may be small, stroke is a serious event. We do not have adequate evidence to reject the null hypothesis of the elevated risk for stroke and cerebrovascular disease in HIV-infected patients with a high HIV RNA viral load. Further follow-up studies with a larger sample size of this subgroup of patients may be warranted.

This study utilized comprehensive EHR data spanning over 10 years from 5 large U.S. health care organizations with diverse populations [35]. We included a large number of vaccination encounters among over 20,000 adults with HIV. Because participating sites deliver integrated care, we were able to ascertain diagnoses of AEs at outpatient, inpatient, and ED settings, and capture CD4+ T-cell counts and HIV RNA viral load measurements at and around the time of vaccination. The SCCS design allowed HIV-infected patients to serve as their own comparison group, minimizing potential confounding caused by certain demographic and clinical risk factors during a relative short follow up. In addition, because we were able to identify all HIV patients who received vaccines of interest during the study period and ascertained the vaccination records and diagnosis of AEs using the comprehensive EHR at all participating sites, our analysis was less likely to be affected by patient selection bias and recall bias that are often concerns for studies that rely on patient recruitment and self-reported vaccination and AEs.

However, there are some potential limitations that should be considered. First, there were no HIV medication data in our study database. However, we investigated HIV medication use among chart-reviewed stroke/cerebrovascular disease cases, and none of the chart-confirmed cases had a documented HIV treatment regimen change around the time of vaccination or the diagnosis. Second, the sample size of HIV-infected patients in stratified analyses might not be adequate to detect a small increased risk of AEs associated with vaccination. Third, although we found that a majority of patients had a stable viral load before and after vaccination, the study could not evaluate whether there were increases in viral load immediately following vaccination, as many patients had CD4+ T-cell count and viral load measured routinely at 3–4 months intervals and measurements during the risk and/or comparison window were not available for some of the patients. The ACIP also recommends Human papillomavirus (HPV) vaccine for HIV-infected persons of 9–26 years old and MenACWY vaccine for all HIV-infected persons to prevent meningococcal disease. Because the sample size of HIV-infected persons of 9–26 years old in the VSD population was small

and the ACIP recommendation for MenACWY for HIV patients occurred after the study period, we did not examine AEs following HPV and MenACWY vaccination.

4.1. Public health implications

Among HIV-infected patients with well controlled HIV disease, routinely recommended inactivated influenza vaccine, hepatitis B vaccines, Td/Tdap, and PPVS23/PCV13 vaccines are generally safe. However, future studies with a larger number of HIV-infected patients with high viral load will likely shed more light on whether there is a substantial elevated risk for stroke and cerebrovascular diseases following those routine vaccinations among those with a HIV RNA viral load greater than 10,000 copies/ml. Nevertheless, given the small absolute risk of stroke and cerebrovascular diseases observed in patients with uncontrolled HIV disease, health-care providers need to evaluate the benefit of vaccination against severe infections and prevent consequent adverse events when considering administering those vaccines for HIV-infected patients with a very high HIV RNA viral load.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The authors thank Sunhea Sylvia Kim, Lindsay Lyons, Sungching Glenn, Christine Taylor, Jo Ann Shoup, Kris Wain, Kate Burniece, Pat Ross, Sandy Bauska, Kristin Goddard, and Berwick Chan for their assistance in obtaining data and conducting chart review for this study.

Sources of funding and support and an explanation of the role of sponsor(s)

This study was funded through the Vaccine Safety Datalink under contract 200-2012-53580 from the Centers for Disease Control and Prevention (CDC). The sponsor reviewed and approved the manuscript and approved submission of the manuscript for publication.

References

[1]. Ho A, Aston SJ, Jary H, Mitchell T, Alaerts M, Menyere M, et al. Impact of HIV on the burden and severity of influenza illness in Malawian adults: a prospective cohort and parallel case-control study. Clin Infect Dis 2017.

[2]. Tempia S, Walaza S, Moyes J, Cohen AL, von Mollendorf C, McMorrow ML, et al. The effects of the attributable fFraction and the duration of symptoms on burden estimates of influenza-associated respiratory illnesses in a high HIV-prevalence setting, South Africa, 2013–2015. Influenza Other Respir Viruses 2017.

[3]. Fine AD, Bridges CB, De Guzman AM, Glover L, Zeller B, Wong SJ, et al. Influenza A among patients with human immunodeficiency virus: an outbreak of infection at a residential facility in New York City. Clin Infect Dis 2001;32 (12):1784–91. [PubMed: 11360221]

[4]. Radwan HM, Cheeseman SH, Lai KK, Ellison IR. Influenza in human immunodeficiency virus-infected patients during the 1997–1998 influenza season. Clin Infect Dis 2000;31(2):604–6. [PubMed: 10987729]

[5]. Meiring S, Cohen C, Quan V, de Gouveia L, Feldman C, Karstaedt A, et al. Infection and the epidemiology of invasive pneumococcal disease (IPD) in South African adults and older children prior to the introduction of a pneumococcal conjugate vaccine (PCV). PLoS One 2016;11(2):e0149104. [PubMed: 26863135]

[6]. Marcus JL, Baxter R, Leyden WA, Muthulingam D, Yee A, Horberg MA, et al. Invasive pneumococcal disease among HIV-infected and HIV-uninfected adults in a large integrated healthcare system. AIDS Patient Care STDS. 2016;30 (10):463–70. [PubMed: 27749111]

[7]. Yin Z, Rice BD, Waight P, Miller E, George R, Brown AE, et al. Invasive pneumococcal disease among HIV-positive individuals, 2000–2009. Aids 2012;26(1):87–94. [PubMed: 22008657]

[8]. Thio CL, Seaberg EC, Skolasky R Jr, Phair J, Visscher B, Munoz A, et al. HIV-1, hepatitis B virus, and risk of liver-related mortality in the multicenter cohort study (MACS). Lancet 2002;360(9349):1921–6. [PubMed: 12493258]

[9]. Troy SB, Rossheim AE, Hilliard DD, Cunningham TD. Brief report: Seroprevalence of pertussis infection in HIV-infected adults in the United States. J Acquir Immune Defic Syndr 2016;73(3): 282–6. [PubMed: 27105050]

[10]. Higgs R, Higgins SC, Ross PJ, Mills KH. Immunity to the respiratory pathogen Bordetella pertussis. Mucosal Immunol 2012;5(5):485–500. [PubMed: 22718262]

[11]. Colebunders R, Vael C, Blot K, Van Meerbeeck J, Van den Ende J, Ieven M. Bordetella pertussis as a cause of chronic respiratory infection in an AIDS patient. Eur J Clin Microbiol Infect Dis 1994;13(4):313–5. [PubMed: 8070437]

[12]. Doebbeling BN, Feilmeier ML, Herwaldt LA. Pertussis in an adult man infected with the human immunodeficiency virus. J Infect Dis 1990;161(6):1296–8. [PubMed: 2189011]

[13]. Vielemeyer O, Crouch JY, Edberg SC, Howe JG. Identification of Bordetella pertussis in a critically ill human immunodeficiency virus-infected patient by direct genotypical analysis of Gram-stained material and discrimination from B. holmesii by using a unique recA gene restriction enzyme site. J Clin Microbiol 2004;42(2):847–9. [PubMed: 14766870]

[14]. CDC. Recommended adult immunization schedule—United States-2014. http://www.cdc.gov/vaccines/schedules/downloads/adult/adult-schedule.pdf Accessed on.

[15]. Kaplan JE, Benson C, Holmes KK, Brooks JT, Pau A, Masur H. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. MMWR Recomm Rep 2009;58(Rr-4):1–207. quiz CE201–204.

[16]. Centers for Disease Control and Prevention (CDC). Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine for adults with immunocompromising conditions: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep. 2012;61(40):816–9. [PubMed: 23051612]

[17]. Bailey CL, Smith V, Sands M. Hepatitis B vaccine: a seven-year study of adherence to the immunization guidelines and efficacy in HIV-1-positive adults. Int J Infect Dis 2008;12(6):e77–83. [PubMed: 18723381]

[18]. Tedaldi EM, Baker RK, Moorman AC, Wood KC, Fuhrer J, McCabe RE, et al. Hepatitis A and B vaccination practices for ambulatory patients infected with HIV. Clin Infect Dis 2004;38(10): 1478–84. [PubMed: 15156488]

[19]. Durham MD, Buchacz K, Armon C, Patel P, Wood K, Brooks JT. Rates and correlates of influenza vaccination among HIV-infected adults in the HIV Outpatient Study (HOPS), USA, 1999–2008. Prev Med 2011;53(1–2):89–94. [PubMed: 21569791]

[20]. Gallagher KM, Juhasz M, Harris NS, Teshale EH. Predictors of influenza vaccination in HIV-infected patients in the United States, 1990–2002. J Infect Dis 2007;196(3):339–46. [PubMed: 17597447]

[21]. Valour F, Cotte L, Voirin N, Godinot M, Ader F, Ferry T, et al. Vaccination coverage against hepatitis A and B viruses, Streptococcus pneumoniae, seasonal flu, and A(H1N1)2009 pandemic influenza in HIV-infected patients. Vaccine 2014;32(35):4558–64. [PubMed: 24951870]

[22]. Koskan AM, Fernandez-Pineda M. Human papillomavirus vaccine awareness among HIV-positive gay and bisexual men: A qualitative study. LGBT Health 2018;5(2):145–9. [PubMed: 29412771]

[23]. Harrison N, Poeppl W, Herkner H, Tillhof KD, Grabmeier-Pfistershammer K, Rieger A, et al. Predictors for and coverage of influenza vaccination among HIV-positive patients: a cross-sectional survey. HIV Med 2017;18(7):500–6. [PubMed: 28035738]

[24]. Sullivan PS, Hanson DL, Dworkin MS, Jones JL, Ward JW. Effect of influenza vaccination on disease progression among HIV-infected persons. Aids 2000;14 (17):2781–5. [PubMed: 11125897]

[25]. Hakim H, Allison KJ, Van De Velde LA, Li Y, Flynn PM, McCullers JA. Immunogenicity and safety of inactivated monovalent 2009 H1N1 influenza A vaccine in immunocompromised children and young adults. Vaccine 2012;30(5):879–85. [PubMed: 22155630]

[26]. Beyer WE, Nauta JJ, Palache AM, Giezeman KM, Osterhaus AD. Immunogenicity and safety of inactivated influenza vaccines in primed populations: a systematic literature review and meta-analysis. Vaccine 2011;29 (34):5785–92. [PubMed: 21624411]

[27]. Ho YL, Brandao AP, de Cunto Brandileone MC, Lopes MH. Immunogenicity and safety of pneumococcal conjugate polysaccharide and free polysaccharide vaccines alone or combined in HIV-infected adults in Brazil. Vaccine 2013;31 (37):4047–53. [PubMed: 23684823]

[28]. Abzug MJ, Pelton SI, Song LY, Fenton T, Levin MJ, Nachman SA, et al. Immunogenicity, safety, and predictors of response after a pneumococcal conjugate and pneumococcal polysaccharide vaccine series in human immunodeficiency virus-infected children receiving highly active antiretroviral therapy. Pediatr Infect Dis J 2006;25(10):920–9. [PubMed: 17006288]

[29]. Flynn PM, Nachman S, Muresan P, Fenton T, Spector SA, Cunningham CK, et al. Safety and immunogenicity of 2009 pandemic H1N1 influenza vaccination in perinatally HIV-1-infected children, adolescents, and young adults. J Infect Dis 2012;206(3):421–30. [PubMed: 22615311]

[30]. Horster S, Laubender RP, Lehmeyer L, Ankerst DP, Eberle J, Reinert R, et al. Influence of antiretroviral therapy on immunogenicity of simultaneous vaccinations against influenza, pneumococcal disease and hepatitis A and B in human immunodeficiency virus positive individuals. J Infect 2010;61 (6):484–91. [PubMed: 20875454]

[31]. Whitaker HJ, Farrington CP, Spiessens B, Musonda P. Tutorial in biostatistics: the self-controlled case series method. Stat Med 2006;25(10):1768–97. [PubMed: 16220518]

[32]. Tseng HF, Sy LS, Qian L, Marcy SM, Jackson LA, Glanz J, et al. Safety of a tetanus-diphtheria-acellular pertussis vaccine when used off-label in an elderly population. Clin Infect Dis 2013;56(3):315–21. [PubMed: 23196953]

[33]. von Elten KA, Duran LL, Banks TA, Banks TA, Collins LC, Collins LC. Systemic inflammatory reaction after pneumococcal vaccine: a case series. Hum Vaccin Immunother 2014;10(6):1767–70. [PubMed: 24642659]

[34]. Package inserts and manufacturers for some US licensed vaccines and immunoglobulins. http://www.vaccinesafety.edu/package_inserts.htm Accessed on: March 22, 2018.

[35]. Sukumaran L, McCarthy NL, Li R, Weintraub ES, Jacobsen SJ, Hambidge SJ, et al. Demographic characteristics of members of the vaccine safety datalink (VSD): A comparison with the United States population. Vaccine 2015;33 (36):4446–50. [PubMed: 26209836]

Table 1

Relative risk (RR) of pre-specified adverse events following vaccination with influenza vaccine, PPSV23 or PCV13, HBV vaccine, and Td or Tdap, Vaccine Datalink Project, 2002–2013.

Adverse event (AE)		Number of AE cases		RR (95% CI)	Adjusted RR* (95% CI)
		Risk window	Comparison window		
Systemic reactions	Anaphylaxis	0	1	N/A	N/A
Local reactions	Cellulitis and infection	355	587	**1.18 (1.03, 1.35)**#	N/A
	Allergic reaction	9	12	1.49 (0.63, 3.53)	N/A
Cardiovascular events	Acute and subacute myocardial infarction	76	131	0.99 (0.75, 1.32)	1.01 (0.74, 1.36)
	Acute pericarditis	3	5	1.01 (0.24, 4.24)	1.65 (0.35, 7.79)
	Acute myocarditis	0	5	N/A	N/A
	Cardiomyopathy	46	81	0.92 (0.64, 1.33)	0.91 (0.61, 1.35)
	Heart failure	62	110	0.94 (0.69, 1.28)	0.96 (0.69, 1.35)
Stroke, cerebrovascular diseases,	Stroke and cerebrovascular diseases	42	89	0.79 (0.55, 1.15)	0.76 (0.51, 1.12)
venous thromboembolism (VTE)	VTE	10	26	0.65 (0.30, 1.39)	0.68 (0.32, 1.46)
Meningitis, encephalitis, and encephalopathy	Meningitis, encephalitis, and encephalopathy	40	58	1.14 (0.76, 1.71)	1.17 (0.76, 1.80)

CI: confidence interval; N/A: not available.

Note: RR was not estimated when there was no AE case during the risk window. The bold font represents the statistically significant RR estimate.

*Adjusted for seasonality for outcomes with risk window ≥ 14 days.

#Risk difference: 6.4 (95% CI: 1.0, 11.8) per 100,000 person-days.

Table 2

Relative risk (RR) of pre-specified adverse events following vaccination among HIV-infected adults with a baseline HIV RNA viral load greater than 10,000 copies/ml, Vaccine Datalink Project, 2002–2013.

Adverse event (AE)		Number of AE cases		RR* (95% CI)
		Risk window	Comparison window	
Systemic reactions	Anaphylaxis	0	1	N/A
Local reactions	Cellulitis and infection	45	75	1.16 (0.80–1.68)
	Allergic reaction	2	4	0.94 (0.17–5.15)
Cardiovascular events	Acute and sub-acute myocardial infarction	5	10	0.58 (0.16–2.03)
	Acute pericarditis	0	0	N/A
	Acute myocarditis	0	1	N/A
	Cardiomyopathy	7	11	1.14 (0.42–3.12)
	Heart failure	6	12	0.80 (0.25–2.52)
Stroke, cerebrovascular diseases,	Stroke and cerebrovascular diseases	11	5	**3.94 (1.32–11.72)**
venous thromboembolism (VTE)	VTE	1	2	N/A#
Meningitis, encephalitis, and encephalopathy	Meningitis, encephalitis, and encephalopathy	9	11	0.98 (0.37–2.57)

CI: confidence interval; N/A: not available.

Note: About 93.5% of the overall sample had a viral load value during the 6 months prior to the vaccination. RR was not estimated when there was no AE case during the risk window.

The bold font represents the statistically significant RR estimate.

*Adjusted for seasonality for outcomes with risk window ≥ 14 days.

#Model failed to converge.

Table 3

Relative risk (RR) of stroke and cerebrovascular diseases following vaccination among HIV-infected adults with a baseline HIV RNA viral load greater than 10,000 copies/ml, by vaccine type, Vaccine Datalink Project, 2002–2013.

Vaccine type	Number of AE cases		RR (95% CI)
	Risk window	Comparison window	
Influenza vaccines (n = 6,693)	7	3	4.3 (0.9–19.7) *
HBV vaccines (n = 1,862)	2	1	2.7 (0.2–30.1)
PPSV23/PCV13 (n = 3,311)	2	1	1.8 (0.1–31.3) *
Td/Tdap (n = 1,300)	1	0	N/A

CI: confidence interval; N/A: not available.

Note: RR was not estimated when there was no AE case during the risk or comparison window.

* Adjusted for seasonality. RR for HBV vaccines were not adjusted for seasonality due to small sample size.

Table 4

Relative risk (RR) of stroke and cerebrovascular diseases following vaccination with influenza vaccine, PPSV23/PCV13, HBV vaccine, and Td/Tdap among HIV-infected adults, based on chart-confirmed new onset and recurrent cases, Vaccine Datalink Project, 2002–2013.

Viral load	Number of cases		Adjusted RR* (95% CI)
	Risk window	Comparison window	
Overall sample	20	46	0.63 (0.36–1.11)
≤200 copies/ml	8	34	0.34 (0.15–0.78)
201–10,000 copies/ml	3	6	0.38 (0.07–2.12)
>10,000 copies/ml	4	4	1.72 (0.41–7.24)#

*RR: RRs were adjusted for seasonality. CI: confidence interval.

#Risk difference: 3.5/1,000,000 person-days, 95% CI: [C0]14–21/1,000,000 person-days.